SCIENCE - Surgery or Cast for Injuries of the EpicoNdyle in Children's Elbows.

A multi-centre prospective randomised superiority trial of operative fixation versus non-operative treatment for medial epicondyle fractures of the humerus in children.

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Chief Investigator: Mr Dan Perry, Daniel.Perry@ndorms.ox.ac.uk

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Joint Research Office, 1st floor, Boundary Brook House Churchill Drive, Headington, OX37GB. ctrg@admin.ox.ac.uk

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Chief Investigator Signature

Statistician Signature

We declare no conflicts of interest.

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Abbreviations

AE – Adverse Event
BNF – British National Formulary
CAT – Computer Adaptive Test
CI – Chief Investigator
CRF – Case Report Form
DSMC – Data and Safety Monitoring Committee
EQ-5D-Y – EuroQol - youth
GCP – Good Clinical Practice
GDPR - General Data Protection Regulation
HE – Health Economy/Economist
HTA- Health Technology Assessment
HRA – Health Research Authority
ICERs - Incremental Cost-Effectiveness Ratios
MAR – Missing At Random
MCID – Minimally Clinically Important Difference
MRC – Medical Research Council
NICE -National Institute for Health and Care Excellence
OCTRU – Oxford Clinical Trials Research Unit
ONS - Office for National Statistics
PACS - Picture Archiving and Communication System
PAG - Parent Advisory Group
PI – Principal Investigator
PSSRU - Personal Social Services Research Unit
PROMIS - Patient Report Outcomes Measurement System
QA – Quality Assurance
QALY – Quality Adjusted Life Year
RCT- Randomised Controlled Trial
REC – Research Ethics Committee
RF – Research Fellow
SAE – Serious Adverse Event
SCIENCE – Surgery or Cast for Injuries of the EpicoNdyle in Children's Elbows
SD –Standard Deviation
SOP – Standard Operating Procedure
TMG – Trial Management Group
TSC – Trial Steering Committee
YPAG - Young Persons Advisory Group

1. Contact details

Clinical Trials Unit: Oxford Trauma
Kadoorie Centre, NDORMS, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU, sciencekids@ndorms.ox.ac.uk 01865 228929

Chief Investigator
Mr Dan Perry, Daniel.Perry@ndorms.ox.ac.uk

Research Manager
Dr Juul Achten, juul.achten@ndorms.ox.ac.uk

Trial Manager
Mrs Louise Spoors, louise.spoors@ndorms.ox.ac.uk

Statistician
Mrs Susan Dutton, susan.dutton@csm.ox.ac.uk

Sponsor
The University of Oxford, Joint Research Office, 1st floor, Boundary Brook House Churchill Drive, Headington, OX3 7GB. ctrg@admin.ox.ac.uk

Funder
National Institute for Health Research, NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), University of Southampton, Alpha House, Enterprise Road, Southampton SO16 7NS, 023 8059 5710.

Trial Management Group

Mr Dan Perry
Dr Juul Achten
Prof James Mason
Prof James Wright
Prof Matt Costa
Dr Duncan Appelbe
Prof Janis Baird
Mr Robert Allen Stevenson
Mr David Ferguson
Dr Liz Tutton
Mrs Louise Spoors
Miss Amrita Athwal
Mrs Susan Dutton
Mr Nicholas Peckham
Dr Ruth Knight
Dr Emma Phelps
Mr Tommy Jess (PPI)
Dr Emma Morley (PPI)
Ms. Jennifer Preston (PPI Manager)

Trial Steering Committee

Mr Michael Whitehouse, University of Bristol (Chair)
0117 4147843, Michael.Whitehouse@bristol.ac.uk

Miss Deborah Eastwood (Independent member)
Dr Catriona McDaid (Independent member)
Mr Dan Perry (Chief Investigator)
Mrs Phoebe Gibson (Independent Lay member)
Miss Georgia Addy (Independent Lay member)

Data and Safety Monitoring Committee

Professor Richard Body (Independent member) (Chair)
0161 2768539, richard.body@manchester.ac.uk

Professor Andreas Roposch (Independent member)
Mr Charlie Welch (Independent member)

2. Summary in Plain English

Why this research?
Broken bones of the elbow are common in children. Doctors have varying opinions about the best treatment for one particular type of elbow break, called a 'medial epicondyle fracture'. Some surgeons argue that these breaks should be treated with surgery to fix the bone with wires or screws, whilst others argue that treating the bone in a cast will give just as good results, without the risks and scars associated with surgery. The research to now is of poor quality and has results supporting both arguments. This means that the treatment that children receive is dependent on the beliefs and understanding of the surgeon, rather than proper science. Perhaps unsurprisingly, half of children in the UK are treated with surgery, and half with a cast. High-quality research is urgently needed to answer this question.

What is the question being asked?
In children with this elbow injury (medial epicondyle fracture), does treatment with surgery result in better arm function after 1 year than treatment without surgery?

What sort of study is it?
The study is called a trial, which is the best method to compare treatments and the best way to get a proper answer. A computer will decide whether a child does or doesn't get surgery – the decision is made between the treatments at random.

How many children will be involved?
Children with this injury are usually around 10/11 years old, though anyone between 7 and 15 years can participate. It is hoped that 334 children will participate over a two year period from more than 35 hospitals. This number is calculated based on previous scientific research to ensure that the study is large enough to reach a firm conclusion.

What will families be asked?
Children, parents and doctors all agree that how well a child can use their arm is the most important thing to find out. This will be measured using a questionnaire that has been developed to measure arm function in children. In addition to arm function, we will also ask questions about sports, pain and quality of life and we will work out the cost of the injury to families and the NHS. Questions will be asked just after the doctors have found out the elbow is broken, and then after 6 weeks, 3, 6 and 12 months. The most important follow-up point is at 12-months, which is called the 'primary outcome'. Parents have advised us to avoid lots of paper documents, instead we will use a website and videos/animations to explain the study, and e-mails and text messages will be used to keep in touch with families. With permission, we will also record the child's NHS number, to look at NHS records in the future to see if they had any future problems with their elbow.

Has there been involvement from families when this research was set-up?
A large group of children and parents, were brought together at Chester Zoo, where they helped to decide 'which' outcomes are important, in addition to 'how' and 'when' to follow-up children. Two parents are directly involved in advising the study on the 'management group', with other parents contributing to the study oversight committee. A group of children who advise researchers on projects (called the GenerationR Young Persons Advisory Group) have helped develop the materials for the study.

3. Synopsis

Study Title	Surgery or Cast for Injuries of the EpicoNdyle in Children's Elbows. A multi-centre prospective randomised superiority trial of operative fixation versus non-operative treatment for medial epicondyle fractures of the humerus in children.		
Acronym	SCIENCE		
Study Registration	The study has been registered with the current controlled trials database under reference number ISRCTN16619778 NIHR CRN Portfolio 41515		
Sponsor	University of Oxford		
Funder	National Institute for Health Research (NIHR)		
Study Design	Multi-centre, multi-surgeon, parallel, two-arm, randomised controlled trial		
Study Participants	Children 7 to 15 years old inclusive with evidence of a medial epicondyle fracture of the humerus.		
Planned Sample Size	334 (167 per arm)		
Planned Study Period	01/10/18 – 31/08/27		
Planned Recruitment Period	01/04/19 – 31/05/21		
	Objectives	Outcome Measures	Time Point
Primary	The primary objective is to quantify and draw inferences on observed differences in **function** using the Patient Reported Outcomes Measurement Information System (PROMIS) Upper Extremity Score for Children between operative fixation versus non-operative treatment at 1 year post-randomisation for fractures of the medial epicondyle in children.	PROMIS	1 Year
Secondary	1. To quantify and draw inferences on observed differences in **function** using the PROMIS Upper Extremity Score between operative fixation versus non-operative treatment. 2. To quantify and draw inferences on **sports and performing arts participation** using the DASH S/PA Module (a validated assessment of higher-level upper limb function) between the	PROMIS DASH S/PA	Week 6, Month 3 & 6 Week 6, Month 3, 6 & 12

	trial treatment groups. 3. To quantify and draw inferences on observed differences in **pain** scores between operative fixation versus non-operative treatment. 4. To quantify and draw inferences on observed differences in **Quality of Life** using EQ5DY (validated assessments of childhood Health-related Quality of Life) between the trial treatment groups 5. To determine the **complication** rate, including the need for further operative fixation. 6. To estimate, the **cost-effectiveness** of the two treatments to the NHS and the broader society. 7. To identify **barriers and facilitators** to recruitment to this study and other paediatric surgical trials. **LONG-TERM OUTCOMES (to be reported separately)** 8. To quantify and draw inferences on **longer-term pain and function,** including the need for further surgery, annually up to 16 years old (the point of skeletal maturity). The need for surgery beyond 16 years old will be measured using NHS number to enable linkage to routine healthcare datasets.	Wong-Baker Faces Pain Score EQ-5DY Complications Healthcare Resource use Child , parent / guardian and staff experiences PROMIS, DASH/PA, EQ-5DY, Linkage to routine datasets	Week 6, Month 3, 6 & 12 Week 6, Month 3, 6 & 12 Week 4 and 6, Month 3, 6 & 12 Month 3, 6 & 12 Pilot phase only Annual
Intervention	Non-operative treatment		
Comparator	Operative Fixation		

4. Introduction

4.1 Background

The management of fractures of the medial epicondyle is one of the greatest controversies in paediatric fracture care[1]. These fractures typically occur in children around 10-12 years old[2], with or without dislocation of the elbow joint. The debate for clinicians is whether to realign and hold the fragments of bone with operative fixation, or whether to allow the fragments to heal in their current position without surgery by resting the elbow in a cast. Observational studies have demonstrated support for both operative and non-operative treatment strategies, which has generated uncertainty amongst surgeons. Two published systematic reviews[2,3], have demonstrated disagreement in the management of this injury. One systematic review concluded that nonsurgical treatment offers excellent functional results equivalent to surgical treatment[3], whilst another concludes that surgical fixation should be strongly considered to achieve union of the bone fragments thereby maximising elbow stability in an increasingly athletic child population[2] . To add further to the debate a widely used 'evidence-based review' textbook has recently advocated against surgery, citing increased long-term pain and stiffness compared to non-operative treatment[4].

Much of the controversy has arisen because there have been no prospective studies evaluating the treatment of these fractures. The current literature has serious methodological limitations, particularly with regard to inconsistent follow-up, no standardisation to the treatment approaches, the infrequent use of patient reported outcomes, and selection bias amongst those selected to undergo operative fixation[4]. Furthermore, there has been a lack of agreement of how to record a successful outcome which heightens the uncertainty; radiographic union of the fracture fragments is the most commonly used outcome in the literature, with pain or function being infrequently recorded, although there is known to be a poor correlation between radiographic union and functional outcomes[3].

The uncertainty within the literature has propagated considerable variation in clinical practice. There is an increasing tendency toward surgery for this fracture, which has been particularly driven by US literature identifying the athletic demands of children and adolescents, and the expectations of patients, parents, and coaches of early mobilisation and return to sport[1,5]. This trend towards surgery is not supported by rigorous research.

4.2 Current Practice

An audit of surgical practice amongst 30 centres in the UK was conducted as part of the feasibility review for this trial, to ascertain practice regarding this injury over a 3-year period, with particular focus on the number of patients treated non-operatively. Data from this audit demonstrated 520 medial epicondyle fractures over this period, 225 (43%) of which

were treated with surgical fixation, and 295 (57%) were treated non-operatively. 39 children had an incarcerated fragment (8%), which is an absolute indication for surgery. This data at minimum demonstrates practice variation for the same injury, and further implies clinical equipoise with regards the best treatment for this injury.

4.3 Evidence why this research is needed now

The clinical management of any fracture depends upon several factors, including the severity of the fracture and the personal characteristics of the patient. These variables are generally out of the control of the treating surgeon. However, the decision to offer 'operative intervention' is highly dependent upon the surgeon, and indeed patients expect their surgeon to advise them in this area.

Not only is there controversy whether to operate on this injury, the indications amongst those receiving surgery vary considerably. There is agreement that in those instances where the fragment of medial epicondyle is trapped in the joint or where the elbow is dislocated and in need of operative intervention to realign the bones, then surgery must be undertaken. However, beyond these relatively rare indications, the usual indication for surgery is radiographic displacement of the fracture fragments beyond a surgeon-dependent threshold that varies between 2mm and 15mm[6,7]; however radiographs on which this assessment is made are known to be hugely misleading with 'minimally displaced' fractures frequently having >10mm displacement evident when using 3D imaging[8,9]. In routine clinical practice 3D imaging is not routinely performed for this injury. In instances whereby the fracture is associated with an elbow dislocation, and the elbow can be relocated with the bones realigned in the emergency department, there is controversy as to whether this necessitates fixation irrespective of the degree of fracture displacement, however a recent systematic review did not find evidence to support the need for surgery in this instance[3]. The degree of displacement, either initially or after healing, has not been shown to affect the outcome of treatment.

Surgical fixation of the medial epicondyle, using either a pin or a screw, is thought to improve the likelihood of 'bony union' of the fracture[2]. However, there are small but definite risks from the surgery including infection, damage to the nerves around the elbow, broken and retained metalwork and the risks associated with general anaesthesia. Whilst possibly increasing the speed of recovery, there is some suggestion that those for whom the fracture has been treated operatively compared with non-operatively may have more long-term pain[10]. Additionally, a second procedure is frequently performed at a later stage to remove the screw/pins used for the fixation owing to skin irritation. The alternative treatment of applying a plaster cast to the elbow does not expose the child to the same surgical risks and has lower costs. However, plaster cast treatment is less likely to result in bony union (approx. 50% vs. 95%)[2], though it is unclear if this has any bearing on functional recovery, including return to sports.

There is therefore a clear and pressing need to inform patients about the benefits or otherwise of operative fixation versus non-operative treatment, and a need to inform commissioners regarding the costs of the different treatment strategies to the NHS and society.

We therefore propose:

A multi-centre prospective randomized superiority trial of operative fixation versus non-operative treatment for medial epicondyle fractures of the humerus in children, using a well-established network of children's orthopaedic surgeons engaged in research.

5. Study design

5.1 Study summary

The proposed project is a two-phased study. Phase 1 (Internal Pilot) will confirm the expected rate of recruitment in a large-scale multi-centre randomised controlled trial. Phase 2 (Main phase) will be the proposed randomised controlled trial in a minimum of 35 centres across the UK.

Internal Pilot

The internal pilot will take place at 20 centres over a period of 12 months. The aim of this initial phase will be to determine the number of eligible and recruited patients in the centres over the course of 12 months as well as to optimise the electronic data collection procedures. Screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion. In addition, the number of eligible and recruited patients, and the number of patients who decline consent or withdraw, will be recorded. Qualitative interviews with parents and children as well as interviews with trial staff will provide further insight into the acceptability of the recruitment process. Depending on the qualitative findings, adjustments to trial information delivery to patients will be made to improve recruitment.

The Data Safety and Monitoring Committee (DSMC) will make a recommendation to the Trial Steering Committee (TSC) regarding trial continuation in the event that the recruitment target for the internal pilot is not met. If the trial is stopped, then all trial patients will be followed up per protocol. If the trial continues into the main phase, patients from the internal pilot will be included in the final analysis.

Main RCT

The main trial will be recruiting from a minimum of 35 centres treating children's fractures across the UK.

Trial Structure

All children aged 7-15 years old presenting at the trial centres with a medial epicondyle fracture of the humerus are potentially eligible to take part in the trial. After consent has been gained, a local research associate will collect baseline demographic data, the Patient Reported Outcomes Measurement Information System (PROMIS) Upper Extremity Score for Children Computer Adaptive Test, DASH S/PA Module, Wong Baker Faces Pain Score, and health-related quality of life using the EuroQoL EQ-5DY.

A randomisation sequence, stratified by centre to account for centre-specific effects, and dislocation-status of the elbow at presentation in the emergency department (i.e. dislocated or not-dislocated) will be produced by the trial statistician. Each patient will be randomly allocated (1:1) to either operative fixation, or non-surgical treatment.

Follow-up will be made electronically (web-link sent by e-mail or text message) for the Patient Reported Outcomes at 6 weeks, 3 months, 6 months and 12 months. The

questionnaires at 3, 6 and 12 months will also contain questions relating to resource use as a result of the child's injury. In exceptional circumstances, data can be collected on paper or via telephone interview. Patient follow-up will be organised centrally.

Patients will then enter a long-term follow-up surveillance phase where a minimal dataset will be requested from them on a yearly basis until skeletal maturity.

5.2 Objectives

The aim of this pragmatic randomised controlled trial is to evaluate the clinical and cost-effectiveness of operative fixation versus non-operative treatment for displaced medial epicondyle fractures of the elbow in children.

5.2.1 Primary objective

To quantify and draw inferences on observed differences in function using the Patient Reported Outcomes Measurement Information System (PROMIS) Upper Extremity Score for Children between operative fixation versus non-operative treatment at 1-year post-randomisation for fractures of the medial epicondyle in children.

5.2.2 Secondary objectives

1. To quantify and draw inferences on observed differences in function using the PROMIS Upper Limb Extremity Score between the trial treatment groups.
2. To quantify and draw inferences on sports and performing arts participation using the DASH S/PA Module (a validated assessment of higher-level upper limb function) between the trial treatment groups.
3. To quantify and draw inferences on observed differences in pain scores using the Wong-Baker faces pain score between the trial treatment groups.
4. To quantify and draw inferences on observed differences in Quality of Life using EQ5DY (validated assessments of childhood Health-related Quality of Life) between the trial treatment groups.
5. To determine the complication rate, including the need for further operative fixation up to 1-year post-randomisation.
6. To estimate, the cost-effectiveness of the two treatments to the NHS and the broader society.
7. To identify barriers and facilitators to recruitment to this study and other paediatric surgical trials.

5.2.3 Long-term Objective (to be reported separately)

To quantify and draw inferences on longer-term pain and function, including the need for further surgery, annually up to 16 years old (the point of skeletal maturity).

5.3 Outcome measures

To ensure the correct outcome domains are being collected, we have undertaken a COMET exercise to ratify the outcomes collected in this trial. A systematic review identified 52

outcome domains that have been previously used to record success/failure in medial epicondyle fractures. A Delphi process considered the views of 25 physiotherapists, 39 UK children's orthopaedic surgeons, 17 surgeons from international orthopaedic trials groups, 20 parents of affected children and 10 affected children. The most important outcome domains are now apparent in the final stages of formalizing the Core Outcome Set.

Core Outcomes Apparent from Delphi Exercise:

- Activities of Daily Living (ability to dress/wash/eat).
- Participation in School Activities
- Ability to resume participation in hobbies and sports.
- Pain
- Complications (Nerve Injury, infection, metalwork prominence, review of any available routinely collected digital images of the elbow stored in the PACS archive).

The primary outcome for this study is functional recovery assessed using the **Patient Report Outcomes Measurement System (PROMIS Bank v2.0) Upper Extremity Score for Children Computer Adaptive Test (CAT)** – PROMIS is a collection of patient-reported health status tools available for children and adults that were developed to be disease nonspecific in collaboration with the US National Institute for Health[11,12]. These tools can be administered to healthy children as well as to children with a variety of chronic health conditions. They are generally self-reported from 8-years old, and proxy-reported below 8-years. The PROMIS Pediatric item banks were developed using a strategic item generation methodology adopted by the PROMIS Network utilising item response theory. Field-testing occurred among 4129 children aged 8 to 17 years old[13]. All raw scores generated from PROMIS instruments are translated into standardized T-scores with a population mean of 50 and a standard deviation (SD) of 10. The population mean refers to the mean of the calibration sample, which, for paediatric and parent proxy instruments, is composed of a higher percentage of patients with chronic illness. Lower T scores indicate a worse outcome for upper-extremity function. PROMIS is available in full (30 questions), short-form (8 questions) or as a computer adaptive test "CAT" (average 8 questions). A CAT enables the answer from one question to inform the choice of the next so each child completing a CAT could answer a distinct set of questions to arrive at their score.

The PROMIS Upper Extremity Score has convergent validity with other tests used in the assessment of arm function in children with congenital limb abnormalities[14], as well as with physiological tests of upper limb function (Grip Strength and Pinch Strength $r>0.6$ $p<0.05$). In the congenital limb population the PROMIS test was also the only tool without ceiling effects (when using the computer adaptive test but not a short form). The PROMIS Upper Extremity Score for Children appears to be the best tool to assess functional recovery in this group of patients. There is now agreement from an international group planning multicentre paediatric orthopaedic trials (IMPACCT), that the PROMIS Upper Extremity Tool is the preferred outcome to assess upper limb function in children. Within the SCIENCE trial, the lowest age of participating children is 7-years old. We are aware that self-reported PROMIS

measures are generally used from 8-years-old, however outcome experts, including the developers of PROMIS, have advised us to use a single version of the questionnaire. Given this, we will collect self-reported function amongst all age children within the trial.

The secondary outcome measures in this trial are:

Sports/ Performing Arts Module of DASH[15] . This is a tool for recording details of sports and performing arts participation relating to upper extremity function. Clinicians and children have both indicated that sports participation must be considered within the analysis. DASH S/PA Module, is distinct from the more general DASH tool that lacks face validity amongst children. Although the DASH S/PA Module was not specifically developed in children, we have worked with our group of patient representatives to ensure that the tool is appropriate for use in children. There was universal agreement amongst patients (i.e. those present at an 'Elbow Study Day' that we held at Chester Zoo, and members of the NIHR Young Persons Advisory Group) that DASH S/PA Module has appropriate langauge to be used amongst children who are able to comprehend other self-reported questionnaires. The DASH S/PA Module therefore has face validity amongst the target population.

Wong-Baker FACES Pain Rating Scale[16]**.** This is a validated self-reported tool. It is an ordinal assessment of pain using a series of six facial-expressions to illustrate the degree of pain intensity. A numerical rating is assigned to each face (from 0, "no hurt" to 10, "hurts worst"). It has been validated for use amongst children over 3 years old, including in the paediatric emergency department[17]; with its use being most established from 5 years-old[18,19]. It has been identified to be an excellent measure of pain when estimating the effect of treatment interventions in the emergency department, and it highly correlated to the visual analogue scale ($r=0.90$ $p<0.001$)[17]. Test-retest reliability is excellent, $r=0.90$, $p<0.001$[20]. The Wong-Baker scale is widely used in clinical practice, forming part of the Royal College of Emergency Medicine 'Composite tool for the assessment of pain in children' produced in 2013 as part of a best practice guideline[21], and was recently specifically highlighted for use by the NICE major trauma guidelines[22].

Quality of life - *EQ-5D-Y*; This is the youth version of the EQ-5D-3L, which is a validated, generalised, health related quality of life questionnaire consisting of 5 domains related to daily activities with a 3-level answer possibility. EQ-5D-Y has been especially adapted in terms of language for children from 8–18 years[23,24]. A proxy version is available for younger children. Its age appropriateness in terms of feasibility, reliability and validity in children and adolescents has been established[24]. There is currently on-going work, to produce EQ-5D-Y value sets for use in children and adolescents. Our interim solution is to apply adult EQ-5D value sets to the EQ-5D-Y classification, but to use the EQ-5D-Y valuation system if ready before the SCIENCE trial is complete. As for PROMIS, given the age of trial participants, we will use the self-reported version of EQ-5D-Y amongst all children in the trial.

Complications - All complications will be recorded. Particular note will be made of complications related to the cast (e.g. pressure areas) or surgery (e.g. wound infection, injury/irritation to the ulna nerve, implant irritation, screw cut-out, broken or retained metalwork and the subsequent need to remove metal pins/ screws). Additionally, any digital images of the elbow that have been collected as part of routine practice will be harvested from PACS at the end of the study. In particular, we will seek to identify images collected pre-operatively, intra-operatively (where relevant) and the last available follow-up image (i.e. the most recent image collected prior to the 1-year primary outcome point - although we acknowledge that this may have been some weeks/months prior to this time-point.) No specific imaging is required at any stage as part of the protocol for this study. Collection of routine digital images as described above has been reviewed by the Radiation Assurance HRA who indicates that the harvesting of routine images in this manner does not constitute exposure to radiation – passing their test "if the radiographs were not available, would the PI require that they took place". Where available, these images will be used to make an assessment of the quality of the reduction, and the presence of bone union.

Healthcare Utilisation – This will be monitored for the economic analysis. Unit cost data will be obtained from national databases such as the BNF and PSSRU Costs of Health and Social Care. Where these are not available the unit cost will be estimated in consultation with the Oxford University Hospitals finance department. NHS costs and patients' parents out-of-pocket expenses will be recorded via a short questionnaire which will be administered at 3, 6 and 12 months post randomisation completed by the parents/guardians.

Throughout the internal pilot phase, completion rates of outcome measures will be carefully monitored. A review of these rates will be discussed by the trial management group on a monthly basis, with potential interventions, such as paper CRF's or reminder phone calls, discussed and implemented prior to the start of the main RCT recruitment phase.

Child, parent/guardian and staff experiences – Children, parent/guardians and staff will be invited to participate in qualitative interviews to share their experience of the SCIENCE study. Interviews will be semi-structured, based on a semi-structured interview guide.

6. Protocol Procedures

6.1 Data Collection.

Complication data will be completed in the routine clinical appointment at 4 weeks. Thereafter, the parent/guardian and/or child will be prompted to complete questionnaires at 6 weeks, 3 months, 6 months, 1-year and annually until 16 years old. Questionnaires will generally be self-reported, however parent/guardian input will be advised when completing health-economic and complication questionnaires. A direct link to the on-line questionnaire will be sent via a text message or email. If the parent/guardian and/or child have not responded to the initial and reminder messages within a specified timeframe (the time allowed will vary for each of the time points), we will attempt to call the parent/guardian to obtain the outcome data for the time point over the telephone. Exact timelines and frequency of phone calls will be specified in the data management plan for this trial. If the parent/guardian cannot be contacted, we may contact the participant's General Practitioner for any complication data relating to the elbow injury, if applicable.

If the parent indicates that a complication or an additional surgery has occurred, the database will be checked to ensure that a complication form has been completed, and if not completed, sites will be prompted to complete this form to give full details of the event.

Once the final questionnaire is completed at the end of year one, a £10 gift voucher will be offered as compensation for any costs (i.e. mobile phone data) incurred whilst completing the outcome measure assessments.

Long-term outcomes

It is believed from discussions with surgeons and patients that functional recovery plateaus after 12-months of follow-up, however the concern in children's orthopaedics is that a longer-term view is necessary, as symptoms may evolve through childhood. We will therefore contact the patients on an annual basis by text message to collect updated PROMIS, DASH S/PA Module, Wong Baker Pain Score, EQ-5DY and Complications until 16 years old; the point at which children have almost universally reached skeletal maturity.

We will collect the NHS number of participants, which we will store securely for 30 years. This will enable the opportunity to collect long-term outcomes using linkage to routinely collected healthcare data to identify interventions on the elbow recorded within routine hospital procedural datasets (i.e. elbow arthroscopy/ elbow arthroplasty). Whilst we will collect and store this information, the future use of this information for linkage will be subject to future ethical/regulatory approvals.

TIME POINT	Data COLLECTION
At Randomisation	PROMIS, DASH S/PA Module, Wong Baker, EQ-5DY.
4 weeks (routine follow-up)	Complications.
6 weeks (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5DY,

	Complications and school attendance.
3 Months (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5DY, Complications, school attendance and economics questionnaire.
6 Months (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5DY, Complications, school attendance and economics questionnaire.
1 Year (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5DY, Complications, school attendance and economics questionnaire.
Annual until skeletal maturity (electronic collection)	PROMIS, DASH S/PA Module, Wong Baker, EQ-5DY, Complications.
Long term (electronic linkage)	Linkage through routine datasets to determine relevant interventions (i.e. elbow arthroscopy/ arthroplasty).

Table 1 Data collection time points

6.2 Sample size

The primary outcome is the Patient Reported Outcomes Measurement Information System (PROMIS) Upper Extremity Score for Children. Raw scores are translated into standardized T-scores with a population mean of 50 and a Standard Deviation (SD) of 10. The 'Minimally Clinically Important Difference' (MCID) for the PROMIS Upper Extremity Score amongst children with milder forms of disability has been demonstrated to be three to four[25]. In general, the bank of paediatric PROMIS measures have an MCID of three points, in a range of different diseases including sickle/asthma/nephrotic syndrome/cancer[26]. During a patient and public involvement event, it was established that whilst a score of 3-4 points appeared to be the minimal difference noticeable to parents, the clinically important difference required to justify surgery was 5 points or more. Parents and children demanded a larger effect size to justify the intervention of surgery. Other studies have similarly highlighted that patients often seek greater effect sizes to warrant surgical interventions than the established MCID[27]. We seek to find a difference of 4 points between the interventions.

The SD of 10 derived by PROMIS was ascertained based on sample of children with a higher proportion of chronic illness than the general population. It is anticipated that the variation in outcomes in the treatment of acute medial epicondyle fractures is likely to be less than in a chronic illness. Therefore, an adaptive trial design, with blinded sample size re-estimation based on the SD of the outcome tool when patient recovery is beginning to plateau, is planned. We will perform the sample size re-estimation calculation after the first the 50 patients have completed 6 months follow-up (estimated to be month nine of the main trial). If, as expected, the standard deviation of the sample is notably less than the chronic disease

population, we will revisit the study timelines to determine the optimal study duration thereby enhancing the efficiency of the trial. In the unlikely event that standard deviation is greater than expected, we will discuss the findings with the trial steering committee to formulate a strategy to meet the increased recruitment target required.

In summary, this study will use the Patient Reported Outcomes Measurement Information System (PROMIS) Upper Extremity Score for Children at 1 year after randomisation as the primary outcome measure. The total number of patients required to obtain a power of 90% to detect a 4-point difference between groups for the primary outcome measure will be 266; i.e. 133 patients will be required in each treatment group. With an allowance for a conservative 20% loss to follow-up, we plan to recruit 334 patients in total. To maximise trial efficiency, we will re-estimate the sample size based on the SD of the outcome tool at 6-months follow-up of the first fifty children in the trial.

6.3 Methodology

6.3.1 Screening and Eligibility

Patients will be eligible for this study if:

- There is radiographic evidence of a displaced medial epicondyle fracture of the Humerus, with fracture displacement determined by the surgeon as per their usual clinical practice.
- They are aged between 7 and 15 years old inclusive.

Patients will be excluded from participation in this study if:

- The injury is more than two weeks old.
- There is incarceration of the medial epicondyle fragment within the elbow joint.
- The injury is part of a complex elbow fracture (i.e. fracture extending into the joint).
- There are other fractured bones elsewhere in the body, in addition to the elbow injury.
- The elbow, if dislocated, is unable to be realigned into a satisfactory position in the emergency department.
- There is evidence that the patient and/or parent/guardian would be unable to adhere to trial procedures or complete follow-up, such as insufficient English language comprehension, developmental delay or a developmental abnormality or no access by parents to the internet.

6.3.2 Recruitment

NHS England Statistics (via NHS digital) have confirmed that there were *601 unique entries* of operative codes indicative of surgical fixation of the medial epicondyle across England in children under 18 years old within the financial year 2015/16. An audit in 30 centres in the

UK demonstrated that 43% of medial epicondyle fracture patients received surgical fixation and the remaining 57% were treated non-operatively. It is important to note that 8% had an incarcerated fragment, which is an absolute indication for surgery. Based on this information we estimate that there are approximately 500-550 potentially eligible cases that are treated operatively per year. In addition, there are at least as many cases treated non-operatively. The total population eligible to participate in this trial is therefore in excess of 1000/year in England alone. It is our intention to recruit patients from at least 35 NHS trusts, including all major paediatric centres, who we anticipate will identify in the region of 600 patients per year for screening purposes. We, anticipate a conservative recruitment of 40-50%, equating to a recruitment rate of 0.5 patients per centre per month.

During the 12-month internal pilot, we expect that between 80 and 120 patients will be recruited from the 20 centres. If less than expected patients are recruited in the pilot phase, the DSMC will provide the TSC with a recommendation with regards the continuation of the study. Following the pilot phase, a minimum of 15 additional sites will be opened and will recruit for 15 months; the total duration of recruitment is therefore 27 months.

6.3.3 Informed Consent

Informed consent will be obtained by the local research associate. A member of the clinical team will approach the patient and their parent/guardian initially about the study. If the patient/parent/guardian is interested they will be introduced to the research associate assigned to the study. The research associate will present the patient with the age-appropriate participant information material (online and/or paper) and verbal explanation of the trial procedures. The patient/parent/guardian will then be given the opportunity to discuss any issues related to the trial with the research associate and members of their family and friends. The parent/guardian will then be asked to sign an electronic informed consent form, and children will be invited to sign an electronic assent form. Assent should be taken where appropriate, however the absence of assent does not exclude the patient from the study if consent has been obtained from the parent/legal representative. If a child completes the assent form indicating that they do not wish to participate, the child will not be included in the study.

Any new information that arises during the trial that may affect participants' willingness to take part will be reviewed by the Trial Steering Committee; if necessary this will be communicated to all participants by the Trial Coordinator. A revised consent form will be completed if necessary.

Qualitative Assessment of Recruitment, and Experience of Treatment Interventions

Qualitative interviews with children, parent/guardians and trial staff will be used to identify barriers and facilitators to recruitment. These will be used to develop practical strategies that can be implemented in the main trial to improve recruitment, which may include changes to the presentation or delivery of study information. We will achieve this by

quantifying: i) parent/guardian, child and surgeons' treatment preferences, ii) reasons for participation or non-participation as reported by parents/guardians and children and iii) barriers to recruitment as identified by staff. Data collected from the interviews will be used to understand: i) staff experience of being involved in a paediatric surgical trial, ii) parent/guardian and children's experience of being asked to participate in a randomised controlled trial and iii) children's experience of the injury, treatment and its consequences in their daily life. Understanding parent/guardian and children's experience of recruitment to this trial may help inform the design of future studies. Understanding children's experience of treatment and recovery may highlight what is important to children when injured and during recovery.

Qualitative Methods

During the pilot study, parents/guardians who were approached about their child's participation in the SCIENCE study (whether or not they participated in the trial), will be invited to be contacted for an interview. Consent will be obtained to permit the qualitative research team to contact parents/guardians. Prior to interview, parents/guardians will receive written (via electronic media or post) and verbal information about participating in an interview, how data is collected, analysed and stored. Consent to participate in the interviews will be obtained by the qualitative researcher. Interviews will be semi-structured and use a brief, flexible topic guide, which enables interviewees to identify what is important to them, and allows topics to be added in response to interviewees' views.

Interviews will be used to explore: i) the parent/guardian's experience of the consent process and study information, ii) their reasons for participation or non-participation and iii) their child's experience of treatment. Interviews will be conducted by an experienced qualitative researcher and last up to sixty minutes. They will be conducted as soon as possible after randomisation to maximise their recall of the consent process. Interviews will be conducted face to face or by telephone, depending on the preference of the participant. All interviews will be audio recorded and transcribed verbatim.

A purposeful sampling strategy will be used, with the intention of interviewing parents/guardians of children in both treatment arms and those who decline participation. We will interview parents/guardians until data saturation is achieved. Based on previous work we estimate that data saturation will be achieved in around 20-25 interviews.

In addition, face-to-face interviews will be undertaken with five children (aged 12 years or over), for whom their parent/guardian can be present. Interviews will be age-appropriate and will explore their experience of: i) injury, ii) the study including the consent process and study materials and iii) treatment.

Healthcare professionals, including participating surgeons, research nurses and research associates, will be asked about their experience of being involved in this study. A researcher

from the SCIENCE team will identify NHS staff to be approached for an interview. NHS staff will initially be invited to interview by phone or email and, if interested, informed consent will be sought. Data from staff will be collected by interview, either individually or in groups, and will explore: i) the study processes such as the procedures for identifying/screening patients, ii) surgeons' views of the interventions and their willingness to randomise patients and iii) staff experience of the consent discussion. We will also seek to identify contextual differences between the centres that may help or hinder recruitment. A purposive sampling strategy will be used to ensure the views of staff from a range of centres are included.

This study involves one surgical and one non-surgical treatment, parents/guardians may have a strong preference or different concerns about the two treatment options. Amongst participants that decline to enter the study, we will review the child and their parent/guardian's preference for treatment collected during screening.

Qualitative data will be managed using NVIVO 10. Data will be analysed inductively, which involves the researcher becoming immersed in the data, then systematically grouping sentences or paragraphs of similar meaning into codes, and searching for themes by comparing across and within codes. The qualitative team will meet regularly during analysis to discuss the emerging themes, with data saturation occurring when the team agree that no new elements are arising from data.

6.3.4 Trial ID

When a patient is randomised, sufficient non-identifiable details will be logged prior to treatment, by the clinical team using a secure, encrypted, web-based system, provided by the Oxford Clinical Trials Research Unit (OCTRU). Basic information including the patient initials, age and eligibility checks will be entered. The patient will then receive a trial ID that will be used on all relevant and non-public facing trial documentation.

6.3.5 Randomisation

The patient will be randomised after consent. All hospital treatment areas have access to the internet so will access the randomisation service in real time i.e. there will be no delay in patient treatment.

Consented children will be randomised to one of two intervention groups (1:1) using a computer randomisation service provided by OCTRU. Randomisation allocation will be implemented using stratification by centre and elbow dislocation status on presentation to the emergency department with randomisation schedules prepared by the trial statistician and embedded in the online system.

Stratification by centre will help to ensure that any clustering effect related to the centre will be equally distributed in the trial arms. The catchment area (the local population served by the hospital) will be similar for all of the hospitals; each hospital being a children's injury unit dealing with these fractures on a daily basis. All of the recruiting hospitals, and indeed all

hospitals throughout the NHS, use these techniques as part of their normal practice i.e. staff will already be equally familiar with both forms of treatment. This cannot eliminate the *clinician-specific effect* of an individual at any one centre[28]. However, since the procedures are commonplace across the NHS, many clinicians will be involved in the management of this group of patients; likely between 5 and 20 clinicians at each centre, including consultants and trainee surgeons. Therefore, we anticipate that each individual clinician will only treat a handful of those enrolled in the trial, reducing the risk of a clinician-specific effect upon the outcome in any one centre.

Stratification by dislocation-status of the elbow (i.e. not dislocated at presentation to emergency department, or dislocated at presentation to emergency department (with a subsequent satisfactory reduction) will help to ensure that the perceived severity of the injuries through additional soft-tissue damage are balanced across the treatment groups to take account of the potential differences in the outcome measures. Any participants that need to go to the operating theatre to have the elbow dislocation reduced, as it is unable to be reduced in the emergency department, will be excluded from the trial.

6.3.6 Pre and Post randomisation withdrawals/exclusions

Children (or their parents/guardians) may decline to continue to take part in the trial at any time without prejudice. A decision to decline consent or withdraw will not affect the standard of care the patient receives. Children (or their parents/guardians) can withdraw by contacting the research team, with contact details on patient information materials and the trial website. Upon withdrawal of the patient, any data collected up until the time of withdrawal will be retained by the research team and included in the final analysis. Contact details for these patients will be destroyed. Withdrawn patients or patients deemed ineligible after consent will not be replaced.

6.3.7 Blinding

Patients and their parents/guardians cannot be blinded to their treatment. The treating clinician will of course, not be blinded to the treatment they are providing. However, the treating clinical team will take no part in the follow-up assessment of the patients. The outcome data will be collected directly from the patient and/or their parents/guardians. Outcome assessors will be blinded to the participant's treatment allocation.

6.4 Technologies assessed

All of the hospitals involved in this trial are familiar with both techniques. All surgeons are proficient in the surgical techniques. All of the patients will receive analgesia at the discretion of the treating clinician as per local guidelines. In the absence of local guidelines, clinicians should adhere to the Royal College of Emergency Medicine best practice guidelines for the management of acute pain in children[21]. If the elbow is dislocated on arrival in the

emergency department, clinicians may attempt to restore the alignment of the elbow using their preferred reduction manoeuvres with appropriate analgesia and/or sedation, as per usual clinical practice.

This trial will compare two approaches to treat displaced medial epicondyle of the humerus in children:

6.4.1 Operative Fixation;

Children are admitted to hospital for surgery, which typically is scheduled on a daytime trauma operating session, though patients can be enrolled irrespective of the time of presentation/ surgery. Children undergo a general anaesthetic. After the skin has been covered in antiseptic, an incision will be made over the medial epicondyle paying particular attention to the location of the ulna nerve. The bone fragments will be opposed in the optimal position achievable under direct vision. A record will be made of the type of fixation used. The bone fragments will be fixed using the preferred technique of the surgeon (i.e. screw/ wire(s)). Although, the basic principles of fixation are inherent in the technique, there are several different options available to the surgeon, with the most common being screw fixation. The type of implant, size and insertion technique are not believed to affect the outcome, and will be left entirely to the discretion of the surgeon as per their normal practice. At the end of the procedure, a sling/plaster/splint/bandage will be applied as per the standard surgical practice. The elbow will be allowed to mobilise as per the usual practice of the treating surgeon under the direction of the clinical team, though fixed immobilisation in a cast should not be used for more than 4 weeks post randomisation.

6.4.2 Non-operative treatment;

This technique involves immobilisation of the elbow to rest the elbow at around 90 degrees of flexion. The immobilisation device (i.e. cast/splint/bandage etc) is not applied with the intention of directly opposing the bone fragments, and therefore the bone fragments will not align perfectly. In this pragmatic trial the duration and method of immobilisation will be left to the discretion of the treating surgeon as per their usual technique, and will be worn as per the standard practice of the treating surgeon. Subsequently, the elbow will be allowed to mobilise as pain allows under the direction of the clinical team. Fixed immobilisation in a cast should not be used for more than 4 weeks post randomisation.

6.4.3 Rehabilitation;

We will ensure that all patients randomised into the two groups will receive the same standardised, written physiotherapy advice detailing the exercises they need to perform for rehabilitation from the point of being able to mobilise. In this pragmatic trial, any other rehabilitation input beyond the written information sheet (including a formal referral to physiotherapy) will be left to the discretion of the treating clinicians. However, a record of

any additional rehabilitation input (type of input and number of additional appointments) together with a record of any other investigations/ interventions will be requested as part of the 4-week, 6-week, 3-month, 6-month, and 12-month follow-up datasets from both patients and clinical teams.

6.5 End of trial

The end of the trial will be defined as the collection/receipt of the last follow-up questionnaire from the last participant.

7. Safety Reporting

7.1 Complications and Serious Adverse Event (SAE) management

Serious adverse events are defined as any *untoward and unexpected medical occurrence that: 'Results in death'*, '*Is life-threatening'*, '*Requires hospitalisation or prolongation of existing inpatients´ hospitalisation'*, '*Results in persistent or significant disability or incapacity'*, '*Is a congenital anomaly or birth defect' or 'any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed'*.

For the purpose of safety recording for this trial, only unexpected serious adverse events (SAEs) potentially related to the intervention will be reported immediately to the Trial Team. When the local research team becomes aware of an unexpected SAE in a trial participant, the Principal Investigator (PI) will review the SAE locally and make a decision about the relatedness of the event to the intervention. If the PI assesses the SAE as potentially related, the details of the event will be entered on a SAE reporting form on the database, and the research team will notify the trial team via email within 24 hours of the PI becoming aware of the event. Once received, causality and expectedness will be confirmed by the Chief Investigator or delegate. SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) within 15 days. All such events will also be reported to the Trial Steering Committee and Data Monitoring Committee at their next meetings.

Complications that are foreseeable in the treatment of these fractures do not need to be reported immediately, provided they are recorded in the 'Complications' section of the Case Report Forms and/or Patient Questionnaires. For this trial, such events include the following complications (including readmission or reoperation to address them) (a) General complications - pressure areas or elbow stiffness, symptomatic instability or non-union of the bone fragments (b) Complications specifically related to surgery - wound infection, injury/irritation to the ulna nerve, implant irritation, screw cut-out, broken or retained metalwork and the subsequent need to remove metal pins/ screws.

8. Data Management

8.1 Data collection and storage

The Case Report Forms will be designed by the trial manager in conjunction with the trial management team. Patients will be asked to provide their contact details as well as the contact details of up to two alternative friends or family members. Experience from numerous orthopaedic trauma trials has highlighted that collection of this additional data reduces loss to follow-up substantially.

Data will be collected in electronic format with direct entry onto the trial database, including the collection of documentary evidence of consent and assent. Electronic data collection has the major advantage of building "data logic" into forms, minimising missing data, data input errors and ensuring the completeness of consent and assent forms. All data entered will be encrypted in transit between the client and server. All electronic patient-identifiable information will be held on a server located in an access controlled server room at the University of Oxford. The data will be entered into a GCP compliant data collection system and stored in a database on the secure server, accessible only to the research team based on their role within the study. The database and server are backed up to a secure location on a regular basis.

Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the public to see on the study website.

Paper forms, if collected, with patient/parent/guardian-identifiable information will be held in secure, locked filing cabinets within a restricted area. The identifiable data will be kept separately from the outcome data obtained from/about the patients (both paper and electronic). Patients will be identified by a trial ID only. Direct access to source data/documents will be required for trial-related monitoring and/or audit by the Sponsor, NHS Trust or regulatory authorities as required. All paper and electronic data will be retained for at least one year after completion of the trial. Contact details will be retained until the long term follow up is complete (when the child reaches skeletal maturity at 16 years of age) and Consent/Assent forms will be kept until the youngest participant reaches 21 years of age.

We will collect the NHS number of participants, which we will store securely for 30 years. This will enable the opportunity to collect long-term outcomes using linkage to routinely collected healthcare data to identify interventions on the elbow recorded within routine hospital procedural datasets (i.e. elbow arthroscopy/ elbow arthroplasty). Whilst we will collect and store this information, the future use of this information for linkage will be subject to future ethical/regulatory approvals.

Audio recordings of qualitative interviews will be electronically transcribed, and the anonymised transcriptions stored on secure servers at the University of Oxford, identified by a trial ID and/or initials only.

The trial will be reported in line with the CONSORT statement and the appropriate extensions including non-pharmacological and patient reported outcomes.

9. Statistics and Analysis

9.1 Statistical Analysis

A separate statistical analysis plan (SAP) with full details of all statistical analyses planned for the data of this study will be drafted early in the trial and finalised prior to any primary outcome analysis. The SAP will be reviewed and will receive input from the Trial Steering Committee (TSC) and the Data and Safety Monitoring Committee (DSMC). Any changes or deviations from the original SAP will be described and justified in the protocol, final report and/or publications, as appropriate. It is anticipated that all statistical analysis will be undertaken using Stata (StataCorp LP, www.stata.com) or other well-validated statistical packages. All analyses will be carried out on the intention-to-treat population (that is all patients will be analysed in the group they were randomized to regardless of actual treatment received. The analyses will be repeated for the per protocol population (patients excluded from the per-protocol population will be pre-specified in the SAP as a sensitivity analysis to test the robustness of the results). Sensitivity analyses that supplement the primary analysis will include repeating the primary analysis for the per protocol population and the as-treated population, bearing in mind that this may introduce bias by losing the benefits of randomisation.

Missing Data: Although we have allowed for up to 20% missing data in the sample size we hope to minimise this by utilising data collection techniques appropriate to the age of participating children. Before carrying out the within trial analysis, we will check the trial data for any missing data. Where possible the reasons for missing data will be ascertained and reported. The nature and pattern of the 'missingness' will be carefully considered — including in particular whether data can be treated as missing at random (MAR). If judged appropriate, missing data will be imputed using multiple imputation. The resulting imputed datasets will be analysed and reported, together with appropriate sensitivity analyses.

Standard descriptive statistics will be used to describe the demographics between the treatment groups reporting means and standard deviations or medians and interquartile ranges as appropriate for continuous variables, and numbers and percentages for binary and categorical variables. All comparative outcomes will be presented as summary statistics and

reported together with 95% confidence intervals and all tests will be carried out at a 5% two-sided significance level.

The Patient Reported Outcomes Measurement Information System (PROMIS) Upper Extremity Score for Children at 12 months is the primary outcome of the study and the primary analysis will compare this between the treatment groups in a linear mixed effects method including all patients, at all time-points and adjusting for the stratification factors. A simple analysis of covariance (ANCOVA) of the primary outcome at 12 months adjusting only for the baseline PROMIS score will be undertaken as a secondary analysis. If the outcome is not normally distributed, non-parametric techniques will be used with no adjustment (for example the Mann-Whitney or the Kruskal-Wallis test).

9.2 Economic evaluation

An economic evaluation of operative fixation versus non-operative treatment will be conducted from the UK NHS and Personal Social Services perspective (PSS)[29] using the SCIENCE trial data.

Health related quality of life will be estimated using the EuroQol EQ-5D-Y[23,24] at baseline, 6 weeks, 3, 6 and 12 months post-randomisation using participant questionnaires. Responses to the EQ-5D-Y will be converted into health preference scores using established methods[30,31]. QALYs will be estimated by integrating the length of life by the utility weights as an 'area under the curve'.

Resource use will be collected over 12 months including the resource use during hospitalisations; for example index primary procedure as well as any additional procedures and re-hospitalisation. A micro-costing approach (theatre material, casts, anaesthesia, theatre time, staff etc.) will be applied to the episode of hospitalisation. Further self-reported questionnaires at 3, 6 and 12 months will inquire about the number of contacts with health services (NHS & private) and the provision of medications.

Out-of-pocket expenses and workdays taken off by parents/carers because of their child's condition will also be asked. A question about time off school will also be included. Since the study participants are children between 7-15 years old, the resource use questionnaires are expected to primarily be filled in by proxies (child's parents/ carers). For adolescents, 14-15 years old we would expect them to be able to self-complete the questionnaire. So, we propose for this age group, to design bespoke questionnaires and pilot them alongside the proxy ones, aiming to further investigate the differences between the two.

The total NHS and PSS cost will be calculated by multiplying resource use data by their unit costs and will be derived from published sources relevant to the UK. Unit costs will be derived from National sources (NHS procurement, PSSRU, BNF, ONS).

Missing data will be explored and managed using similar methods to the main statistical analysis.

An incremental cost-effectiveness analysis, expressed in terms of incremental cost per quality-adjusted life year (QALY) gained will be performed using bivariable regression. Results will be presented using incremental cost-effectiveness ratios (ICERs), net benefit and value of information. Further, sensitivity analyses will consider the broader issue of the generalisability of the study results, including a broader societal perspective to include out-off pocket expenses borne by participants' parents, informal care provided by family and friends and parents' income loss.

10.Trial Oversight

The trial will be conducted in accordance with the Medical Research Council's Good Clinical Practice (MRC GCP) principles and guidelines, the Declaration of Helsinki, Oxford Clinical Trials Research Unit SOPs, relevant UK legislation and this Protocol. GCP-trained personnel will conduct the trial.

The day-to-day management of the trial will be the responsibility of the Trial Manager, supported by the OCTRU administrative staff. This will be overseen by the Trial Management Group, who will meet monthly to assess progress. It will also be the responsibility of the Trial Manager to undertake training of the research staff at each of the trial centres. The trial statistician, health economist and the information specialist will be closely involved in setting up data capture systems, design of databases and clinical reporting forms. A TSC and a DSMC will be set up.

10.1 Study Committees

The Trial Management Group which is made up of the Investigators listed in Section 1 and staff working on the project within OCTRU. A TSC and DSMC, each with an independent Chairperson, will also be set up.

The TSC, which includes independent members provides overall supervision of the trial on behalf of the funder. Its terms of reference will be agreed with the HTA and will be drawn up in a TSC charter which will outline its roles and responsibilities. Meetings of the TSC will take place at least once a year during the recruitment period.

An outline of the remit of the TSC is to:

- monitor and supervise the progress of the trial towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DSMC
- inform the funding body on the progress of the trial.

The DSMC is a group of independent experts external to the trial who assess the progress, conduct, participant safety and, if required critical endpoints of a clinical trial. The study DSMC will adopt a DAMOCLES charter which defines its terms of reference and operation in relation to oversight of the trial. They will not be asked to perform any formal interim analyses of effectiveness. They will, however, review accruing data, summaries of the data presented by treatment group, and will assess the screening algorithm against the eligibility criteria. They will also consider emerging evidence from other related trials or research and review related SAEs that have been reported. They may advise the chair of the Trial Steering Committee at any time if, in their view, the trial should be stopped for ethical reasons, including concerns about participant safety. As stated in Section 4.5 a sample size re-estimation is planned, the DSMC will review this. DSMC meetings will be held at least annually during the recruitment phase of the study. Full details including names will be included in the DSMC charter.

11.Quality Assurance

11.1 Quality control

We will institute a rigorous programme of quality control. The trial management group will be responsible for ensuring adherence to the trial protocols at the trial sites. Quality assurance checks will be undertaken by the CTU to ensure integrity of randomisation, study entry procedures and data collection. The CTU has a quality assurance manager who will monitor this trial by conducting regular (at least once in the lifetime of the study, more if deemed necessary) inspections of the Trial Master File. Furthermore the processes of consent taking, randomisation, registration, provision of information and provision of treatment will be monitored. Written reports will be produced for the TSC, informing them if any corrective action is required.

Additionally, the study may be monitored, or audited by sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

11.2 Risk Assessment

A risk assessment will be completed prior to the start of recruitment. Re-evaluation of the risk assessment will be performed after significant changes to the protocol.

12. Finance and Insurance

12.1 Funding

This study is funded by the National Institute for Health Research Health Technology Assessment (17/18/02).

12.2 Insurance and Indemnity Arrangements

The Sponsor has a specialist insurance policy in place – Newline Underwriting Management Ltd, at Lloyd's of London – which would operate in the event of any participant suffering harm as a result of their involvement in the research. Standard NHS cover for negligent harm is in place for NHS procedures. There will be no cover for non-negligent harm.

12.3 Contractual Agreement

A contract will be drawn up between the Department of Health and the University of Oxford. Further collaboration agreements will be completed between the University of Oxford and the Universities of Warwick and Southampton as well South Tees and Alder Hey NHS trusts.

13. Ethical and Regulatory Considerations

13.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3 Approvals

The protocol, informed consent form assent form, participant information material and other study materials will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4 Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the General Data Protection Regulation (GDPR) and the Data Protection Act, which requires data to be de-identified as soon as it is practical to do so.

13.6 Expenses and Benefits

A £10 gift voucher will be offered for participation in the research project. These funds are offered to compensate for any cost and inconvenience participant families may have incurred by using their mobile phone or computer to complete the outcome measure assessments.

13.7 Ethical considerations

The two interventions used in this study are both standard clinical practice and currently offered to patients across the UK. Surgeons therefore have community equipoise.

We are aware that being part of a study, particularly a study involving randomisation, may be a concern for some parents. We are working closely with the NIHR-funded TRECA (Trials Engagement in Children and Adolescents) team at the University of York. They have a wealth of experience in the preparation of documentation presented to parents and children to maximise the quality and accessibility of information provided to families. In addition, the research associates at the recruiting sites have all got extensive experience in working with children and parents.

Recompense for data costs caused considerable debate amongst our PPI forum (through the NIHR Young Persons Advisory Group and Parents Advisory Group). It was recognised that cost may be a barrier to participation for some families (i.e. particularly those from more deprived groups, who frequently use pay-as-you-go data tariffs); whilst others believed that automatically offering recompense for participation would be a barrier to them – as they believed the NHS could ill-afford to make such payments. Agreement was therefore made to offer a payment of £10 to cover reasonable out of pocket expenses, rather than for this to be automatically provided. We have incorporated this approach in our trial.

Patient information materials have been written to broadly appeal to children and parents/guardians. We have discussed this content in detail with the NIHR young persons advisory group (YPAG - who principally range in age between 11 and 16 years old), parents advisory group (PAG), health care professional and our PPI advisors and Jenny Preston (who leads PPI across NIHR CRN Child)). The online content is an extensive package of multimedia content which children and parents agreed was readily accessible to all. Online content is readily available in all locations, and is optimised for different device viewing (i.e. mobile vs. desktop). To supplement this content, it was felt that a single simplified information leaflet may be useful for sites to use (at their discretion) to frame the conversation around consent. Parent co-applicants and members of the Parents Advisory Group have identified the key information that they wish to have available in this simplified document, and which they would like to be able to access only online (i.e. some elements of data protection and GDPR). We will ensure that the full trial details (i.e. in a conventional PIS format) are available for download on the trial website in a parent and child format.

14. Publication Policy

The study monograph will be prepared by the trial management team at the completion of the trial. No patient/parent/guardian identifiable information will be contained in any form of dissemination of study results.

Dissemination will be via traditional and novel methods:

- Conference: Traditional conference dissemination will focus on presentations to include the key professional stakeholders (orthopaedic surgeons, emergency medicine doctors, emergency nurse practitioners and trainees in orthopaedic surgery and emergency medicine).
- Publications: Key outputs will be published in high-impact journals with publicity sought in other professional journals (e.g. Pulse, HSJ, Nursing Times). We will ensure that plain English summaries are published alongside the full paper, along with links to other digital media on the trial website to explain the trial result in an accessible format – i.e. an explainer video and infographic. Given the frequency of the injury, this is also likely to be of interest to international press-outlets.
- Policy Makers: We will ensure the development of links with key organisations such as NICE, NHS Information Centre, NHS England and Quality Observatories to contribute to and capitalise on their networks. Most importantly the outputs will directly contribute to the NICE non-complex fracture guidelines, and will be directly relevant to the widely publicised Choosing Widely Campaign.
- Public Dissemination: To ensure a broad campaign we will target a range of social media outlets (e.g. twitter and blogs such as MumsNet) with the explainer video and infographic. We will seek to engage the NHS Dissemination centre, and seek to publish 'digital story' as part of the 'NIHR Signal'. Finally, will produce a Wikipedia page for this injury (currently absent) and update this with the trial result.

15. Development of a New Product/Process or the Generation of Intellectual Property

Not applicable

16. Archiving

Documents will be archived as per the appropriate standard operating procedures as prepared by the Oxford Clinical Trials Unit.

17. Project Timetable and Milestones

This is a 48 months study starting in March 2019 and reporting in October 2022. The trial will thereafter be extended to Autumn 2027 when results of the long-term follow-up will be reported. The planned trial timetable is shown below, with key milestones indicated and the responsible parties identified:

Month	By date	Activity	Milestone	Responsibility
-4-0		Ethics submission	REC approval	CI/RF
0-6	Oct 2018	Start study	1st TSC/DSMC meeting	CI/TM
	Feb 2019	Complete study set-up	Protocol-CRF approval sponsor/REC	TMG
	March 2019	Achieve CTU 'Green Light'	CRF final version	CI/TS/TM
6-17	April 2019	Start pilot recruitment	1st trial site open for recruitment	CI/TM
	Oct 2019		All 20 pilot sites open for recruitment	CI/TM
	Feb 2020	End pilot recruitment	TSC make recommendation to progress to full trial	CI/TSC
18-22	Mar 2020	Start recruitment at main trial sites	1st main trial site open for recruitment	CI/TM
	Jul 2020		All 35 main sites open for recruitment	CI/TM
18-32	May 2021	Complete recruitment	334 patients recruited	
33-44	May 2022	Complete follow-up all sites	All patients completed 12 months follow-up	
45-48	July 2022	Analyses		HE/TS
		Reporting		TMG
	Sept 2022	Main trial phase close-down	Final TSC/DSMC meeting	CI/TM
49	Oct 2022		HTA report	TMG
56	May 2023	Long term follow-up	Yearly long term follow-up completion*	CI/TM
68	May 2024		Yearly long term follow-up completion*	CI/TM
80	May 2025		Yearly long term follow-up completion*	CI/TM
92	May 2026		Yearly long term follow-up completion*	CI/TM
104	May 2027		Yearly long term follow-up completion*	CI/TM
106	July 2027	Analysis	Analyse clinical effectiveness data	TS
107	Aug 2027	Report	Manuscript submission	TMG

*CI Chief Investigator, DSMC Data and Safety Monitoring Committee, HE Health Economics, RF Research Fellow, TS Trial Statistician, TM Trial Manager, TMG Trial Management Group, TSC Trial Steering Committee.*Total numbers to be followed per year will be confirmed at the end of the recruitment period – numbers will depends on recruitment rate and age of the patients at the time of recruitment.*

18. Protocol Amendments:

Amendment No.	Date of Amendment	Date of Approval
None to date		

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